Hyperammonemia in ICU patients: A frequent finding associated with high mortality

To the Editor:

Hyperammonemia usually develops because of acute liver failure (ALF) or chronic liver disease (CLD), but it may occur in the absence of hepatic disease (non-hepatic hyperammonemia, NHH). Hyperammonemia may induce encephalopathy, which can range from mild cognitive disturbances to coma, cerebral edema, brain stem herniation, and death [1]. Critically ill patients constitute a population where several risk factors for NHH are present [2,3]. Despite this fact, studies on incidence and possible etiologies of this disorder in this population are lacking.

We conducted a prospective observational study in a medical–surgical intensive care unit (ICU) and in a burn ICU of the Londrina University Hospital (Londrina, PR, Brazil) between March 2012 and September 2012. All adult patients aged ⩾18 years admitted to these ICUs were included (n = 258). Exclusion criteria were ALF, CLD, death within the first 24 h of admission, patients discharged from the ICUs within 48 h of elective surgery, or lack of signed informed consent. The local ethics committee approved the study and all research subjects (or their surrogates) provided written informed consent before being included in the study.

Arterial ammonia levels were collected at admission and on the third, seventh, fourteenth, twenty-first, and twenty-eighth days after admission and were analyzed together with severity scores, admission diagnostics, and predisposing factors for NHH. Blood samples were stored in ice, centrifuged within 30 min, and analyzed by an enzymatic method with glutamate dehydrogenase as the reagent [4]. Patients were classed as hyperammonemic if their ammonia levels were above 35 μmol/L at any time. NHH was further classified as mild (36–99 μmol/L) and severe (⩾100 μmol/L) [5].

Demographics, admission diagnostics (classified as sepsis, multiple trauma, burn injury, post-operative state, lymphoma/leukemia/multiple myeloma, and other), and APACHE II [6] score were obtained at the ICU admission. The SOFA [7] score was calculated at admission and every subsequent day. The conditions considered risk factors for NHH and investigated on a daily basis are presented in Table 1.

After exclusions (n = 158), one hundred patients remained in the study, 22 of them with burn injuries. Seventy-three patients presented hyperammonemia, which was classified as mild in 60 cases and severe in 13 cases. Hyperammonemia was observed in 40% of patients in the first day of ICU stay and by the 3rd day of ICU stay, cumulative incidence of NHH reached 60%. Ammonia levels ranged from 36 to 1616 μmol/L (median 57 μmol/L). Only thirteen out of the 73 NHH patients presented risk factors for the condition (2 valproic acid and 2 carbamazepine use, 3 gastrointestinal hemorrhage, 1 with UTI due to urease-splitting organisms, 1 with urinary diversion, and 4 with convulsions).

Cox regression analysis using patients' characteristics at admission did not indicate any statistically significant association among NHH, admission diagnostics, age, and severity scores. Associations of NHH with possible risk factors and other conditions present on the day of hyperammonemia appearance are presented in Table 1. NHH occurrence was statistically associated with the SOFA score and prolonged fasting.

Mortality rates were statistically significant (χ^2 test; p <0.01 for comparison between all groups) between patients with severe (10/13, 76.92%) and moderate hyperammonemia (25/60, 41.67%) and between this last group and patients without hyperammonemia (3/27, 11.11%).

Urea cycle disorders rarely cause NHH in adults and usually present with much higher ammonia levels (only one patient in our series had very high ammonia levels). Patients with ALF and CLD were excluded from this study and serum bilirubin levels were not associated with the occurrence of hyperammonemia; however, we could not exclude specific harm to hepatic ammonia clearance systems since aminotransferases were only dosed if indicated by the ICU staff and did not figure in the statistical analysis. When liver capacity is surpassed due to increased ammonia production and/or reduced ammonia degradation, kidneys, muscles and central nervous system (in a much smaller scale), increase their participation in ammonia detoxification [8]. In our study, the estimated glomerular filtration rate was similar in patients with and without NHH but urinary ammonia excretion was not studied. Regarding muscle tissue, the positive association between NHH and prolonged fasting seen in this study could be linked to fasting-induced muscle protein breakdown with the utilization of amino acids for gluconeogenesis [9], resulting in increased substrate for ammonia generation. Another possible explanation is provided by Görg *et al.*, which demonstrated, in a murine model of sepsis, that the enzyme glutamine synthetase is both down-regulated and inactivated due to tyrosine nitration induced by LPS infusion [10].

In conclusion, the present study demonstrated, for the first time, the incidence of NHH in ICU patients. It occurred early and frequently, and it was associated with increased mortality, high SOFA scores, and fasting. Risk factors commonly ascribed to the condition were uncommon, and statistical analysis did not find a correlation between them and NHH appearance. The detailed pathogenesis of NHH in critically ill patients and whether NHH contributes to patient mortality or it is merely an epiphenomenon of severe illness are matters for further research. Nevertheless, the present findings should encourage the investigation for NHH in critically ill patients, as it is a potentially life-threatening, treatable disorder.

Conflict of interest

The authors who have taken part in this study declared that they do not have anything to disclose regarding funding or conflict of interest with respect to this manuscript.

Table 1. Risk of hyperammonemia development based on patient characteristics on the day of its appearance.

	NHH		HR (95% CI)
	Yes	No	
Number	73	27	
Age	51 (24.7-66.7)	63 (42-74)	0.994 (0.984-1.005)
Gender (Male)	48 (65.8%)	13 (48.1%)	1.413 (0.864-2.312)
SOFA (72/27)	6 (3-10.7)	3 (1-5)	1.082 (1.026-1.141)*
Total bilirubin >2.0 mg/dl	7/67 (10.4%)	0/26 (0%)	2.038 (0.922-4.507)
INR (40/12)	1.28 (1.19-1.69)	1.16 (0.98-1.46)	1.445 (0.693-3.015)
eGFR <60 ml/min/1.73 m^2	29/73 (39.7%)	12/26 (46.2%)	0.837 (0.519-1.352)
Urea mg/dl (48/13)	43 (26.2-93.7)	57 (28-88.5)	0.997 (0.991-1.003)
Corticosteroid	28/73 (38.4%)	7/27 (25.9%)	1.297 (0.807-2.083)
Valproic acid	1/73 (1.4%)	0/27 (0%)	2.310 (0.319-16.722)
Carbamazepine	0/73 (0%)	3/27 (11.1%)	0.047 (0.000-15.064)
Total calories[a,b] Cal/d (62/12)	774 (0-1512)	1023 (496-1480)	1.000 (0.099-1.000)*
Total nitrogen[a,b] g/d (62/12)	4,95 (0-9,7)	6.5 (3.15-9.42)	0.957 (0.915-1.001)
Glutamine	11/73 (15.1%)	0/27 (0%)	1.192 (0.626-2.272)
Prolonged fasting[c]	19/73 (26.0%)	1/27 (3.7%)	2.308 (1.332-3.999)*
Convulsions	1/73 (1.4%)	0/27 (0%)	2.310 (1.332-3.999)
Urinary diversion[d]	1/73 (1.4%)	0/27 (0%)	2.310 (0.319-16.722)
Urinary tract infection[e]	0/73 (0%)	0/27 (0%)	
GI hemorrhage	0/73 (0%)	0/27 (0%)	
Chemotherapy	0/73 (0%)	0/27 (0%)	

Univariate Cox regression analysis. Frequencies and percentages for categorical variables, medians and interquartile range for continuous variables. In first column, in parenthesis, after SOFA, INR, urea, total calories, and total nitrogen, the number of patients from the groups with and without NHH, respectively, that had the parameter available for analysis on the day of onset of hyperammonemia.

SOFA, Sequential Organ Failure Assessment; INR, international normalized ratio; eGFR, glomerular filtration rate estimated by the 4 variable MDRD equation; GI, gastrointestinal.

[a]Patients only receiving oral diet were not included.

[b]Recorded as the sum of either enteral or parenteral nutrition.

[c]Fasting for $\geqslant$24 h.

[d]Ileal conduit in the only patient.

[e]UTI by urea splitting organisms.

*p <0.05.

Authors' contributions

F.A.P.; Conception and design of the study; data acquisition, analysis and interpretation; drafting of the manuscript. V.D.A.D.; Conception and design of the study; data acquisition, analysis and interpretation; drafting of the manuscript. C.M.C.G.; Conception and design of the study; data acquisition, analysis and interpretation; drafting of the manuscript. J.A.O.; Conception and design of the study; data acquisition, analysis and interpretation; drafting of the manuscript. All authors critically revised and approved the final version of the article to be published.

References

[1] Butterworth RF. Effects of hyperammonaemia on brain function. J Inherit Metab Dis 1998;21:6–20.

[2] Walker V. Severe hyperammonaemia in adults not explained by liver disease. Ann Clin Biochem 2012;49:1–15.

[3] Clay AS, Hainline BE. Hyperammonemia in the ICU. Chest 2007;132:1368–1378.

[4] Barsotti RJ. Measurement of ammonia in blood. J Pediatr 2001;138:S11–S20.

[5] Bernal W, Hall C, Karvellas CJ, Auzinger G, Sizer E, Wendon J. Arterial ammonia and clinical risk factors for encephalopathy and intracranial hypertension in acute liver failure. Hepatology 2007;46:1844–1852.

[6] Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: a severity of disease classification system. Crit Care Med 1985;13:818–829.

[7] Vincent JL, Moreno R, Takala J, et al. The SOFA (Sepsis-related Organ Failure Assessment) score to describe organ dysfunction/failure. On behalf of the Working Group on Sepsis-Related Problems of the European Society of Intensive Care Medicine. Intensive Care Med 1996;22:707–710.

[8] Olde Damink SWM, Deutz NEP, Dejong CHC, Soeters PB, Jalan R. Interorgan ammonia metabolism in liver failure. Neurochem Int 2002;41:177–188.

[9] Pozefsky T, Tancredi RG, Moxley RT, Dupre J, Tobin JD. Effects of brief starvation on muscle amino acid metabolism in nonobese man. J Clin Invest 1976;57:444–449.

[10] Görg B, Wettstein M, Metzger S, Schliess F, Häussinger D. Lipopolysaccharide-induced tyrosine nitration and inactivation of hepatic glutamine synthetase in the rat. Hepatology 2005;41:1065–1073.

Fabrizio A. Prado*

Department of Internal Medicine, Londrina State University, Rua João Wycliff, 405, Londrina, PR, Brazil

*Corresponding author.

E-mail address: fabrizioalmeidaprado@gmail.com

Vinicius D.A. Delfino

Department of Internal Medicine, Londrina State University, Rua Walter Motta Campos 293, Londrina, PR, Brazil

Letters to the Editor

Cintia M.C. Grion
Department of Internal Medicine, Londrina State University, Rua Vila. Lobos 580, Londrina, PR, Brazil

Jair A. de Oliveira
Department of Pathology, Clinical Analysis and Toxicology, Londrina State University, Avenida do Café 655, Londrina, PR, Brazil